1. Scientific Abstract

Study title: The safety and antiviral efficacy of cellular adoptive immunotherapy with autologous $CD8^+$ HIV-specific cytotoxic T cells combined with interleukin-2 for HIV seropositive individuals.

Studies of the contribution of individual host immune responses in controlling virus replication have identified a crucial role for $CD8^+$ class I MHC-restricted cytotoxic T lymphocytes (CTL), although the natural host response rarely curtails virus replication completely. Our lab has utilized the adoptive transfer into HIV seropositive individuals of unmodified and genetically modified autologous $CD8^+$ HIV-specific T cell clones which have been expanded ex vivo, to evaluate the therapeutic potential of augmenting host CTL activity and to study mechanisms of virus evasion. This study has demonstrated that the administration of large numbers (up to $3.3 \times 10^9/m^2$) of $CD8^+$ HIV-specific CTL is safe, augments HIV-specific cytolytic activity in vivo, and is associated with a dramatic reduction in circulating HIV-infected $CD4^+$ T cells. The LN retrovirus which encodes neomycin phosphotransferase was introduced into the CTL clones to provide a marker gene to track persistence and migration of the infused CTL. The CTL clones were shown to migrate to lymph nodes and localize adjacent to cells replicating HIV (Attached manuscript - Section 6. Appendix). However, the adoptively transferred HIV-specific CTL persisted at high levels for < 7 days and the antiviral effect was transient.

In vitro studies have demonstrated that after activation through the antigen receptor, $CD8^+$ HIV-specific CTL require IL-2 or $CD4^+$ Th cells to proliferate and survive. HIV seropositive individuals are typically deficient in $CD4^+$ HIV-specific Th responses presumably because of the propensity for $CD4^+$ T cells responding to HIV antigens to become infected and be eliminated. Thus, the adoptively transferred CTL although able to localize to sites of infection and eliminate infected cells, may fail to persist because of a lack of T cell help. In the proposed study, we will evaluate the coadministration of IL-2 by daily subcutaneous injection with transferred $CD8^+$ HIV-specific CTL clones to determine if in vivo persistence of transferred CTL can be improved and if the antiviral effect of this therapy can be prolonged. In our prior study we developed an in situ hybridization assay (ISH) to detect neo sequences that were amplified by PCR in fixed cells and this allowed a quantitation of LN-marked CTL in the peripheral blood and lymph nodes using flow cytometry (Attached MS - Section 6. Appendix). Thus, in the proposed study we will again use the LN retrovirus to mark $CD8^+$ HIV-specific CTL given with the first two infusions. The first infusion will be given without IL-2 and will be followed 7 days later by a second infusion with subcutaneous IL-2 for up to 14 days. The frequency of LN marked cells in the blood after the first and second infusions will be evaluated by flow cytometry to provide a sensitive means for detecting an effect of IL-2 on the persistence of transferred CTL in peripheral blood. If the first two infusions and the IL-2 are tolerated and IL-2 improves T cell persistence, a third infusion of unmarked CTL will be given with a longer course of IL-2. The study will involve up to 24 patients to allow us to determine if a dose of IL-2 that can be safely administered with CTL and improve T cell persistence can be identified. The LN retrovirus used to mark the CTL in this study is identical to that used in our previous study (RAC 9508-119).